Comparing Differential Tissue Harmonic Imaging With Tissue Harmonic and Fundamental Gray Scale Imaging of the Liver

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Objective. The purpose of this study was to compare fundamental gray scale sonography, tissue harmonic imaging (THI), and differential tissue harmonic imaging (DTHI) for depicting normal and abnormal livers. ***Methods.*** The in vitro lateral resolution of DTHI, THI, and sonography was assessed in a phantom. Sagittal and transverse images of right and left hepatic lobes of 5 volunteers and 20 patients and images of 27 liver lesions were also acquired. Three independent blinded readers scored all randomized images for noise, detail resolution, image quality, and margin (for lesions) on a 7-point scale. Next, images from the same location obtained with all 3 modes were compared blindly side by side and rated by all readers. Contrast-to-noise ratios were calculated for the lesions, and the depth of penetration (centimeters) was determined for all images. ***Results.*** In vitro, the lateral resolution of DTHI was significantly better than fundamental sonography ($P = .009$) and showed a trend toward significance versus THI ($P = .06$). In the far field, DTHI performed better than both modes ($P < .04$). In vivo, 450 images were scored, and for all parameters, DTHI and THI did better than sonography ($P < .002$). Differential tissue harmonic imaging scored significantly higher than THI with regard to detail resolution and image quality ($P < .001$). The average increase in penetration with THI and DTHI was around 0.6 cm relative to sonography ($P < .0001$). The contrast-to-noise ratio for DTHI showed a trend toward significance versus THI ($P = .06$). Side-by-side comparisons rated DTHI better than THI and sonography in 54% of the cases ($P < .007$). ***Conclusions.*** Tissue harmonic imaging and DTHI do better than fundamental sonography for hepatic imaging, with DTHI being rated the best of the 3 techniques. ***Key words:*** differential tissue harmonic imaging; liver; sonography; tissue harmonic imaging.

Abbreviations
CNR, contrast-to-noise ratio; DTHI, differential tissue harmonic imaging; RFA, radio frequency ablation; THI, tissue harmonic imaging; VAS, visual analog scale

Received April 30, 2007, from the Department of Radiology, Taipei Veterans General Hospital, and School of Medicine, National Yang-Ming University, Taipei, Taiwan (S.Y.C.); and Department of Radiology, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania USA (F.F., T.B.F., L.N.). Revision requested May 29, 2007. Revised manuscript accepted for publication July 2, 2007.

This study was supported by an equipment loan from Toshiba America Medical Systems (Tustin, CA).

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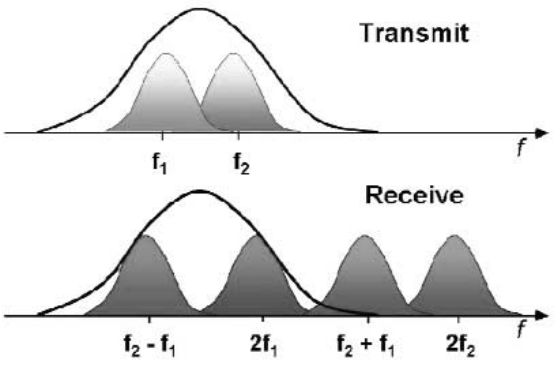
Sonography is often one of the first imaging studies for evaluation of the liver because it is simple, inexpensive, and noninvasive. Recent advances in ultrasound technology, such as tissue harmonic imaging (THI), have made ultrasound even more widely used in liver imaging than previously.[1–3]

In fundamental gray scale sonography, the same frequency spectrum that is transmitted into the patient is subsequently received (albeit modified by attenuation) to produce the sonographic image. In THI, higher harmonic frequencies (multiples of the fundamental frequency) generated by the nonlinear propagation of the ultrasound beam through tissues are used to produce the

image.[4–7] Currently, it is generally the second harmonic, or twice the fundamental frequency, that is used for imaging because of the limited bandwidth of the transducer. Because the beam width for the second harmonic component is narrower than that of the fundamental beam, the lateral resolution of THI is superior to that of conventional gray scale sonography.[4] Tissue harmonic imaging also provides a better signal-to-noise ratio and reduced side lobe artifacts, resulting in better performance in scanning obese patients and patients with poor acoustic windows.[4–7]

Recently, pulse inversion harmonic imaging was suggested as a new technique for enhanced detection of microbubble-based sonographic contrast media.[8–10] This technique cancels first harmonic signals by transmitting a pulse sequence where each pulse is an inverted copy of the previous pulse because the sum of echoes from subsequent pulses will be zero under linear scattering conditions. Hence, echoes from stationary tissue will be suppressed. However, nonlinear echoes associated with contrast microbubbles will not cancel out and can thus be preferentially detected and displayed as in wideband harmonic imaging.[8] The pulse inversion technique is also used to improve suppression of fundamental signals in nonlinear imaging modes, such as THI, that do not require contrast agents.

Figure 1. The principle of DTHI. A dual-frequency pulse (centered around f_1 and f_2) is transmitted (top). The received signal (bottom) will contain echoes at the sum and difference of the 2 transmitted frequencies (ie, $f_2 + f_1$ and $f_2 - f_1$) as well as at their higher harmonics ($2f_1$ and $2f_2$). Only the lower-frequency components will fall within the transducer's bandwidth (ie, $f_2 - f_1$ and $2f_1$).



A new nonlinear sonographic imaging technique, differential tissue harmonic imaging (DTHI) has recently been released commercially (by Toshiba America Medical Systems, Tustin, CA). In the DTHI mode, a dual-frequency pulse is transmitted (Figure 1), which can be expressed mathematically as

$$\sin \omega_1 t + \alpha \sin \omega_2 t, \tag{1}$$

where ω_1 (= $2\pi f$) and ω_2 are the 2 angular frequencies used. Nonlinear propagation in a viscous medium such as tissue can be described, according to the KZK (Khokhlov-Zabolotskaya-Kuznetsov) equation,[11,12] by the following term:

$$\begin{aligned} \frac{\partial}{\partial t}\{(\sin \omega_1 t + \alpha \sin \omega_2 t)^2\} &= \sin 2\omega_1 t \\ &- 2\alpha \sin(\omega_2 - \omega_1)t \\ &+ 2\alpha \sin(\omega_2 + \omega_1)t \\ &+ \sin 2\omega_2 t. \end{aligned} \tag{2}$$

The received signal (ie, the solution to Equation 2) can be seen to include echoes at the sum and difference frequencies of the 2 transmit pulses as well as at their harmonic frequencies. Suppression of fundamental signals is achieved with pulse subtraction (a technique similar to pulse inversion). Differential tissue harmonic imaging is designed to combine the advantages of fundamental gray scale sonography with that of conventional THI, especially at larger depths (>8 cm).

The purpose of this study was to conduct a prospective, blinded evaluation of DTHI for imaging of normal liver tissue and liver abnormalities compared with conventional THI and fundamental gray scale sonography with respect to image quality and general diagnostic capabilities, as well as an in vitro evaluation of the lateral resolution of the 3 imaging modes.

Materials and Methods

In Vitro Study

Ultrasound examinations were performed by an experienced sonographer using an Aplio scanner (Toshiba America Medical Systems) with a broad-bandwidth (1–6 MHz) curvilinear transducer (PVT-375BT). The lateral resolution of fundamental sonography, THI, and DTHI was

assessed in vitro with a tissue-mimicking phantom (model 539; ATS Laboratories, Inc, Bridgeport, CT) with embedded monofilament nylon wires. Different imaging parameters were applied, including depths of 12, 15, and 17 cm and focal zone placements of 4, 6, 10, and 13 cm, without or with zoom for visualization of the wires. Digital still images were acquired in all 3 modes with the same gain setting, dynamic range, focal zone, zoom mode, and depth of field and saved on the scanner's hard disk. The horizontal length of the wires (in millimeters) at the focal zone and in the near/far field (ie, at depths of <8 or >8 cm) was measured on the scanner (with the built-in calipers) by 3 independent observers.

Subjects

The in vivo study was a prospective clinical trial conducted from March to August 2006 involving 25 adults (5 healthy volunteers and 20 patients). The enrolled subjects were 21 years or older. The 20 clinical patients were identified by the investigators from a population scheduled to undergo radio frequency ablation (RFA) of liver tumors at our institution. The study was approved by the university's Institutional Review Board and was compliant with the Health Insurance Portability and Accountability Act. All patients who met the inclusion criteria over the study period and who were willing to participate received a written and verbal explanation of the trial and gave written informed consent before enrollment in the study.

This study was supported in part by Toshiba America Medical Systems. The sponsor provided the Aplio scanner. The authors of this article had sole control of the data generated by this trial and the information provided for publication.

Ultrasound Examinations

All enrolled subjects underwent ultrasound examinations of the liver consisting of fundamental sonography, THI, and DTHI. The dynamic range was fixed at 60 dB for all images. The fundamental frequency used throughout this study was 5.0 MHz, whereas the THI transmit/receive frequency pair was 2.0/4.0 MHz. The dual frequencies transmitted in the DTHI mode were 3.0 and 6.0 MHz. For each set of images, that is, images acquired with all 3 modes for the same anatomic location or hepatic lesion, the focal zone and scanning depth were adjusted (in the fundamental sonographic mode) to optimize visualization of the target region and kept constant. No compounding or other image-processing techniques were applied. The time-gain compensation and 2-dimensional overall gain setting for each image were optimized individually for each imaging technique. Sagittal and transverse still images of both lobes of the liver were obtained in all subjects with fundamental sonography, THI, and DTHI. Imaging of the right hepatic lobe was focused at the bifurcation of the anterior and posterior branches of the right portal vein. Imaging of the left hepatic lobe was focused at the umbilical portion of the left portal vein and caudate lobe. In subjects with hepatic lesions, including volunteers with incidental hepatic lesions and patients scheduled for RFA of liver tumors, additional still images of the hepatic lesions were acquired in the sagittal and transverse planes. Digital images were recorded before being transferred to a personal computer for offline analysis.

Data Analysis

The in vitro lateral resolution of each mode was evaluated by comparing the horizontal length of the wires in the phantom measured by the 3 observers. Evaluation of the in vivo sonographic images (all 3 modes) was conducted offline by 3 blinded and independent observers using a 7-point visual analog scale (VAS) from 1 (worst) to 7 (best) to rate the following image features: noise, detail resolution, image quality, and margin (for lesions only). All of the images were cropped to remove any information related to the scanning parameters and presented in random order for scoring. After the initial scoring had been completed for all images, a side-by-side comparison of each image set (ie, of images from the same location obtained with all 3 modes) was also conducted to determine which mode achieved the best image for demonstration of normal liver tissue, hepatic lesions, or both. A VAS ranking of the 3 modes was recorded from 1 (best) to 3 (worst) by the 3 observers independently and blindly (again without any information as to which image was recorded in which mode).

Two quantitative parameters were also determined, specifically the maximal depth of penetration (read by the observers; in centimeters) and the contrast-to-noise ratio (CNR). The latter was calculated in subjects with focal hepatic lesions or liver tumors as follows[13,14]:

$$\text{CNR} = \frac{2(\mu_A - \mu_B)^2}{\sigma_A^2 + \sigma_B^2}, \quad (3)$$

where μ denotes the mean echo levels; σ denotes the SD of the echo levels; and the subscripts A and B indicate homogeneous image regions of the abnormality and background, respectively. Data were obtained with ImagePro Plus software (Media Cybernetics, Silver Spring, MD) from the maximal circular region that could be placed within the hepatic lesion and circular regions of the same size located in the adjacent background. Two background areas adjacent to the hepatic lesion were used, and the final CNR values were computed as the average of the CNRs obtained from the 2 background areas.

The comparison of the in vitro lateral resolution of each mode was performed with a two-way ANOVA (analysis of variance) and Stata 8.0 (Stata Corporation, College Station, TX), with $P < .05$ considered significant. The analysis was repeated with the data split by near and far fields. In vivo CNRs and the increase in the depth of penetration were also analyzed with an ANOVA. The nonparametric Wilcoxon signed rank test was used to analyze the performance of the 3 different modes according to the VAS scoring of each imaging feature and the side-by-side ranking of the 3 modes. The interobserver variability was analyzed by calculating intraclass correlation coefficients.[15]

Results

In vitro, the lateral resolution of DTHI was significantly better (ie, smaller) than that of fundamental sonography (difference, 0.44 ± 1.00 mm; $P = .009$) based on 39 measurements. Differential tissue harmonic imaging also showed a trend toward a statistically significant improvement in lateral resolution compared with THI (difference, 0.38 ± 1.25 mm; $P = .06$). In the far field (n = 21), the lateral resolution of DTHI was better than that of both fundamental sonography and THI ($P < .04$). In the near field (n = 18), the lateral resolution of both DTHI and THI was better than that of sonography; however, there was no statistical significance for DTHI compared with THI ($P = .14$).

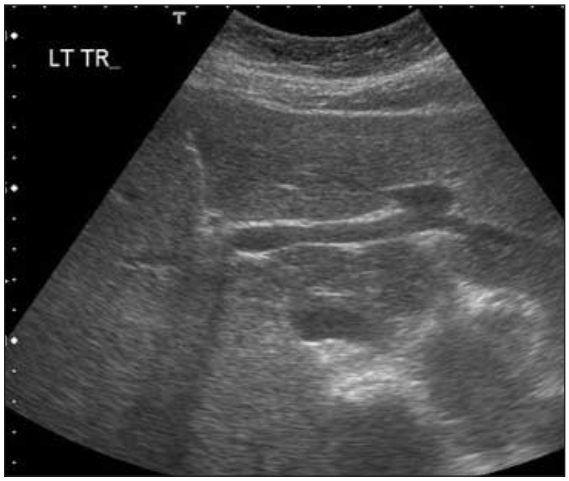
One hundred fifty sets of images (ie, in triplicate) were obtained from the 25 subjects in this study, including 98 sets of normal anatomic locations (Figure 2) and 52 sets of hepatic lesions (Figure 3). Each set of images contained the 3 different modes evaluated: fundamental sonography, THI, and DTHI. In total, 450 images were scored by the 3 readers. Images of 27 hepatic lesions were obtained from 21 individuals with 1 to 4 hepatic lesions. There were 17 patients with 1 hepatic lesion, 3 patients with 2 hepatic lesions, and 1 patient with 4 hepatic lesions. The 156 images of hepatic lesions were also scored for tumor margins.

For all parameters assessed, fundamental sonography scored significantly worse than both THI and DTHI ($P < .002$; Table 1). Moreover, the DTHI scores were significantly better than those of THI with regard to detail resolution and image quality ($P < .001$). The average depth of penetration in both the THI and DTHI modes was significantly better (deeper) than that in fundamental sonography ($P < .0001$; Table 2). The mean increases in penetration with THI and DTHI relative to fundamental sonography were 0.54 ± 1.95 and 0.61 ± 1.96 cm, respectively. There was no significant difference in the depth of penetration between the DTHI and THI modes ($P = .41$).

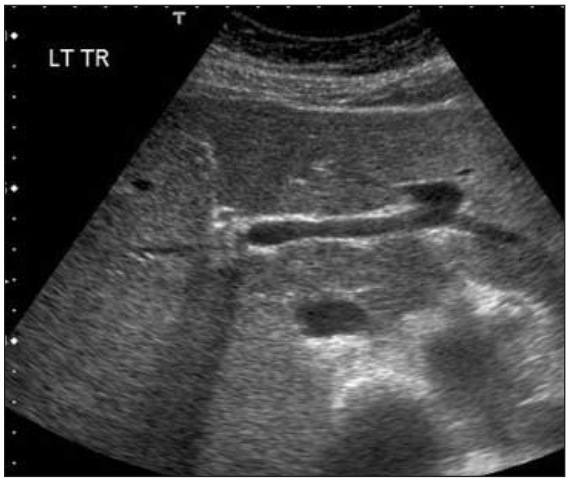
The CNR for the 52 hepatic lesions is shown in Table 2. Among the 3 modes, DTHI achieved the highest average CNR (3.48), followed by fundamental sonography (3.39) and then THI (2.94). However, only the difference between DTHI and THI showed a trend toward significance ($P = .057$), whereas the other differences were not statistically significant ($P > .23$). The results of the side-by-side comparison of the 3 imaging modes are listed in Table 3. The overall ranking showed that DTHI was considered significantly better than THI and fundamental sonography ($P < .01$). Moreover, THI scored statistically higher than fundamental sonography ($P < .0001$). Overall, DTHI scored the best in 241 cases, THI in 172 cases, and fundamental sonography in 37 cases of the 450 image sets (3 readers each scored 150 image sets), which is equivalent to 54% (241/450), 38% (172/450), and 8% (37/450), respectively.

Figure 2. Examples of normal transverse scans of the left lobe of the liver showing the portal vein in the fundamental sonographic (**A**), THI (**B**), and DTHI (**C**) modes.

A



B



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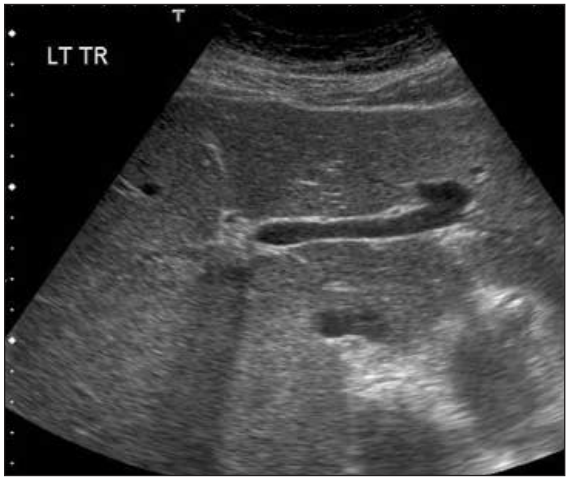
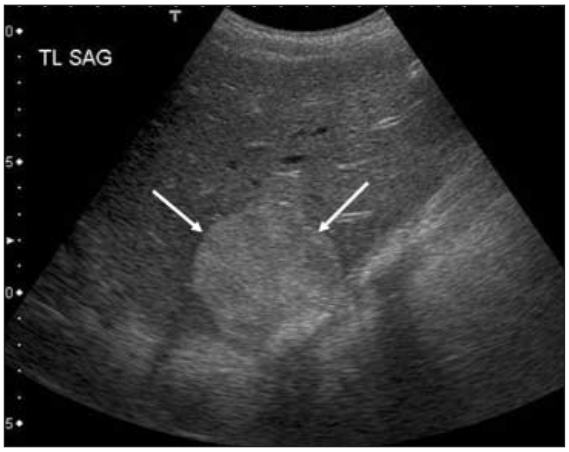


Figure 3. Examples of sagittal scans of a hepatic metastasis (arrows) from a carcinoid tumor scheduled for RFA therapy visualized in the fundamental sonographic (**A**), THI (**B**), and DTHI (**C**) modes.

A



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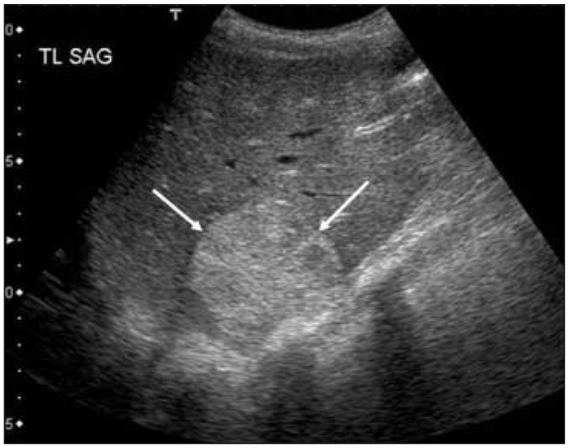

C

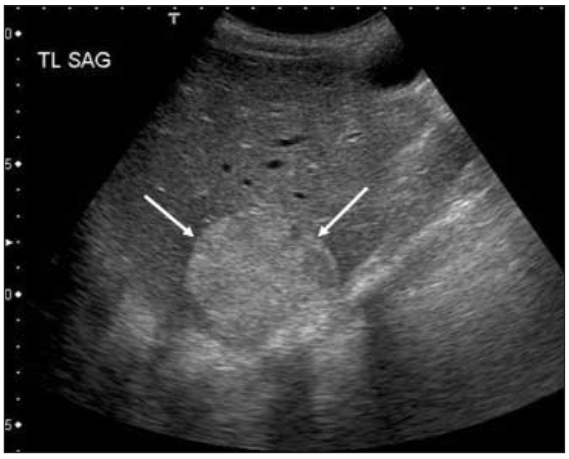

Table 1. Average Score of the Parameters Assessed in the 150 Sets of Images (Including 52 Sets of Hepatic Lesions) by All 3 Readers

Parameter	Sonography	THI	DTHI
Noise	4.34 ± 1.44*	5.06 ± 1.25	5.06 ± 1.32
Detail resolution	4.03 ± 1.54*	4.55 ± 1.32	4.78 ± 1.43†
Image quality	4.19 ± 1.54*	4.77 ± 1.29	4.95 ± 1.37†
Margin (of lesions)	4.17 ± 1.88*	4.59 ± 1.57	4.73 ± 1.65

*Sonography versus THI and sonography versus DTHI: $P < .002$.
†Differential tissue harmonic imaging versus THI: $P < .001$.

The level of agreement between the 3 readers was assessed with intraclass correlation coefficients, which ranged from 0.31 (for margins assessed with THI) to 0.77 (for margins assessed with fundamental sonography). When evaluated by modality, the ranges were 0.60 to 0.77, 0.31 to 0.53, and 0.44 to 0.56 for fundamental sonography, THI, and DTHI, respectively.

Discussion

This study was designed to evaluate 3 sonographic modalities, fundamental gray scale sonography, THI, and DTHI, for depicting normal liver tissue and focal hepatic lesions. In our study, the overall assessment confirmed that THI and DTHI were significantly better than fundamental sonography with respect to noise, detail resolution, image quality, and margins of lesions ($P < .002$; Table 1 and Figure 1). Moreover, DTHI did achieve significantly higher in vivo scores than THI for detail resolution and image quality ($P < .001$). However, unlike the in vitro results, DTHI did not have greater penetration than THI in vivo ($P = .41$), presumably because of the complex liver background in vivo and the subjective nature of VAS readings. We speculate that this may also be the reason why both nonlinear imaging modes achieved greater penetration than fundamental sonography ($P < .0001$; Table 2). It should be noted that DTHI was designed to have improved penetration due to the lower-frequency components included in this mode.

In the side-by-side comparison of the 3 modes, DTHI and THI were both ranked significantly better than fundamental sonography ($P < .0001$; Table 3). More importantly, DTHI was also ranked better than THI ($P = .006$). While simultaneously reviewing images from the 3 different modalities scanning the same area, the observers could better assess the overall image quality and make relative comparisons than when assigning a score to each image individually. Nonetheless, the results of the side-by-side comparison were compatible with the results obtained for the individual parameters, in which DTHI scored better than THI with respect to detail resolution and image quality.

Many clinical studies have shown that THI provides additional diagnostic information in hepatic sonography compared with conventional gray scale sonography.[5–7,10,16–18] Hann et al[16] reported on their experience with THI of the liver compared with conventional sonography of the liver. They found that THI provided the same information as sonography in 71% of their 48 patients and added information in 29% of the patients. Seventeen percent of patients had lesions revealed by THI only. Jang et al[10] evaluated 97 focal hepatic lesions with pulse inversion harmonic imaging, THI, and sonography. In their study, THI was judged superior to sonography in evaluating cysts ($P < .05$) but was not considered beneficial for solid hepatic lesions ($P > .15$), unlike the results of our study. Pulse inversion harmonic imaging showed the best conspicuity and also enhanced characteristics of both cystic and solid hepatic lesions ($P < .05$). Tanaka et al[17]

Table 2. Quantitative Results for Penetration (for 150 Sets of Images) and CNR (for 52 Sets of Hepatic Lesions) by All 3 Readers

Parameter	Sonography	THI	DTHI
Penetration, cm	10.6 ± 2.28*	11.1 ± 2.14	11.2 ± 2.17
CNR, arbitrary unit	3.39 ± 3.27	2.94 ± 3.07†	3.48 ± 4.14

*Sonography versus THI and sonography versus DTHI: $P < .0001$.
†Differential tissue harmonic imaging versus THI: $P = .057$.

Table 3. Side-by-Side Ranking of the 3 Imaging Modes (Best to Worst, 1–3) in the 150 Sets of Images by All 3 Readers

Sonography	THI	DTHI
2.73 ± 0.60*	1.71 ± 0.63†	1.56 ± 0.66

*Sonography versus THI and sonography versus DTHI: $P < .0001$.
†Tissue harmonic imaging versus DTHI: $P = .006$.

evaluated 100 randomly arranged liver images of THI and sonography in 50 patients. Their prospective study showed that THI was statistically more effective for detection of focal lesions ($P < .05$), particularly in cirrhotic livers ($P < .02$). Sodhi et al[7] reported on 50 patients with focal hepatic lesions and concluded that THI was better than conventional sonography for fluid-solid differentiation, detail, and total image quality in focal hepatic lesions, especially in obese patients and patients with poor acoustic windows.

Our study not only confirmed the improved performance of THI compared with fundamental sonography but also indicated the potential benefits of the new nonlinear imaging technique DTHI. In our study, DTHI was subjectively scored best among the 3 modes with regard to certain parameters, and it did best in the quantitative evaluation of in vitro lateral resolution. In vivo, DTHI achieved the deepest penetration and the highest CNR values, although only the improvement in penetration relative to fundamental sonography was statistically significant. The side-by-side comparison also showed that the readers preferred DTHI to THI and sonography for evaluation of the normal liver and hepatic lesions.

In conclusion, DTHI and THI provide better hepatic images and better penetration than fundamental sonography. Differential tissue harmonic imaging is superior to THI in detail resolution and image quality and produces better CNRs for focal hepatic lesions. Among the 3 sonographic techniques, DTHI was rated best by the observers. Our study suggests that DTHI has the potential to provide better sonographic images of the liver and to further improve the image quality of hepatic sonography.

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